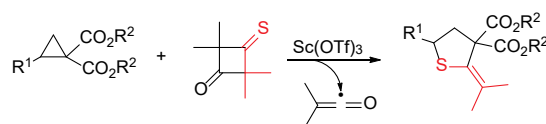


Formal Insertion of Thioketenes into Donor-Acceptor Cyclopropanes by Lewis Acid Catalysis

André U. Augustin,[†] Marius Busse,[†] Peter G. Jones,[‡] Daniel B. Werz^{†,*}

[†]Institute for Organic Chemistry and [‡]Institute for Inorganic and Analytical Chemistry, TU Braunschweig, Hagenring 30, 38106 Braunschweig, Germany

Supporting Information Placeholder



ABSTRACT: Donor-acceptor cyclopropanes were reacted under Lewis acid catalysis with 3-thioxocyclobutanones as surrogates for disubstituted thioketenes. A broad scope of 2-substituted tetrahydrothiophenes with a semicyclic double bond was obtained under mild conditions, with high functional group tolerance and in excellent yield. A sequence of a formal [3+2]-cycloaddition followed by a subsequent release of disubstituted ketene is postulated as the mechanism.

In the recent past donor-acceptor (D-A) cyclopropanes have become a center of attention in organic synthesis as valuable three-membered building blocks. Even though the pioneering work by Wenkert and Reissig took place in the 1970s and 1980s,¹ only in the last decade they have been extensively utilized by many groups to access complex carbo- and heterocyclic scaffolds and have even been employed in natural product synthesis.² The vicinal arrangement of donor and acceptor substituents in combination with a high ring strain of about 115 kJ/mol explains why they commonly react with 1,3-zwitterionic character,³ and this special behavior paves the way for numerous transformations. Whereas cycloaddition processes⁴ have been the most popular, rearrangements⁵ and ring-opening reactions⁶ by either nucleophiles, electrophiles or radicals have also been investigated.

Within the broad variability of possible reactions, Stoltz and coworkers reported a Lewis acid-mediated [3+2]-cycloaddition of D-A cyclopropanes with heterocumulenes under mild conditions. Isocyanates, isothiocyanates and carbodiimides undergo efficient insertion in a chemoselective manner to form the respective five-membered heterocycles (Scheme 1a).⁷ Very recently, Yang extended this method to the insertion into γ -butyrolactone-fused cyclopropanes to obtain single stereoisomers of the corresponding thioimides and amidines,⁸ whereas Wang showed an elegant intramolecular cross-cycloaddition of allenes linked to cyclopropane 1,1-diester to afford [4.3.0]bicyclononane and [3.2.1]bicyclooctane scaffolds.⁹

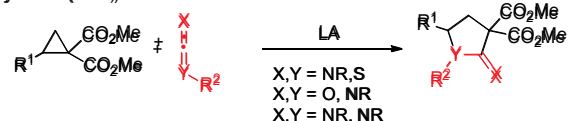
Based upon these results, we were keen to test whether a formal thioketene insertion into D-A cyclopropanes is able to deliver similar sulfur analogs (Scheme 1b). Because thioketenes are rather unstable and only a few examples have been reported,¹⁰ we turned our attention to 3-thioxocyclobutanones as suitable surrogates for disubstituted thioketene moieties. From our recent

studies we know that thioketenes can be inserted into the polarized three-membered ring systems.¹¹ Thus, we proposed that tetrahydrothiophene scaffolds with a semicyclic double bond should arise from an analogous process with D-A cyclopropanes via a formal [3+2]-cycloaddition followed by a [2+2]-cycloreversion, releasing disubstituted ketene.

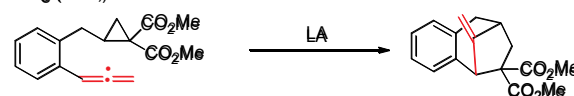
Scheme 1. [3+2]-Cycloaddition

a) Previous work

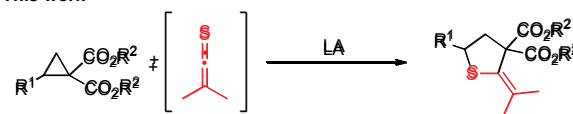
by Stoltz (2012)



by Wang (2013)



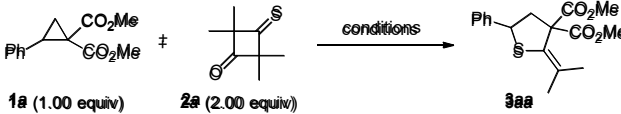
b) This work



To start our investigations, we used D-A cyclopropane **1a** and 3-thioxocyclobutanone **2a** as model substrates. Initial reactions were carried out in dichloromethane at 60 °C. Whereas AlCl₃, MgI₂ and Zn(OTf)₂ as Lewis acid showed no conversion, product formation was observed with Sn(OTf)₂ and Yb(OTf)₃ in moderate yield (Table 1, entries 1-5). Subsequently, other common Lewis acids have been subjected to the reaction conditions, whereby Sc(OTf)₃ seemed to be the most promising catalyst

with an initial product formation of 95% yield (Table 1, entry 6). Changing the solvent to toluene resulted in a complex mixture, while THF showed no conversion of cyclopropane **1a** (Table 1, entries 7-8). Using dichloroethane as solvent was invaluable and delivered the desired product **3aa** in quantitative yield (Table 1, entry 9). As shown in entry 10, decreasing the reaction temperature to 40 °C was detrimental to product formation.

Table 1. Optimization of the Reaction Conditions^a



entry	Lewis acid	solvent	temp (°C)	yield (%)
1	AlCl ₃	CH ₂ Cl ₂	60	0
2	MgI ₂	CH ₂ Cl ₂	60	0
3	Zn(OTf) ₂	CH ₂ Cl ₂	60	0
4	Yb(OTf) ₃	CH ₂ Cl ₂	60	47
5	Sn(OTf) ₂	CH ₂ Cl ₂	60	31
6	Sc(OTf) ₃	CH ₂ Cl ₂	60	95
7 ^b	Sc(OTf) ₃	toluene	60	complex mixture
8 ^b	Sc(OTf) ₃	THF	60	0
9 ^b	Sc(OTf) ₃	DCE	60	quant
10 ^{b,c}	Sc(OTf) ₃	DCE	40	0

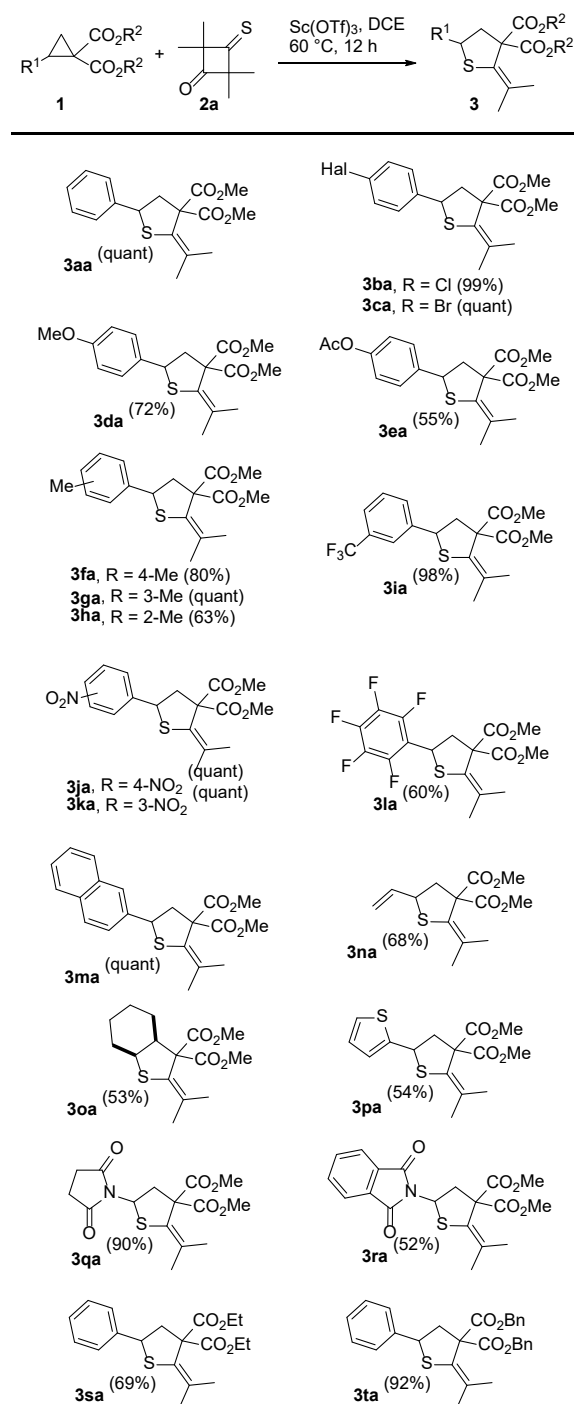
^aReaction conditions: **1a** (100 μmol), **2a** (200 μmol), Lewis acid (10 mol %), solvent (2.5 mL), under Ar, 16 h, yields represent isolated and purified products, ^b12 h, DCE = dichloroethane, ^conly formation of intermediate **4aa** was observed

With the optimized conditions in hand we explored the generality of our protocol. Thus, we subjected various D-A cyclopropanes **1** to the standard procedure. As shown in Scheme 2, a broad variety of starting materials was tolerated. Phenyl substituents bearing halogens undergo the reaction with similar outcome (**3ba-3ca**), whereas methoxy or acetoxy attached to the phenyl donor show slightly less product formation (**3da-3ea**). Methyl substituents in *ortho*, *meta* and *para* position afforded **3fa-3ha** in up to quantitative yield. Even trifluoromethyl-substituted aryl moieties (**3ia**) and other markedly electron-poor phenyl units (**3ja-3ka**) furnished the desired products in excellent yield. The transformation also proceeded smoothly with the highly electron-deficient perfluorophenyl donor in a respectable yield of 60% (**3la**). Increasing the π -system to a naphthyl residue generated the desired product **3ma** quantitatively, while decreasing the π -character to a vinyl donor leads to a less efficient transformation (**3na**). Decoration of the three-membered ring with annulated cyclohexyl (**3oa**) or thienyl (**3pa**) residues provided the desired products in moderate yield, while nitrogen donors gave products **3qa-3ra** in up to 90% yield. Besides dimethyl ester acceptors, diethyl- and dibenzyl-substituted acceptors have been shown to undergo the reaction in good yields (**3sa-3ta**).

We then investigated the outcome of the reaction on using different 3-thioxocyclobutanones. Those could be accessed from the corresponding acyl chlorides by a two-step procedure including ketene formation under basic conditions followed by

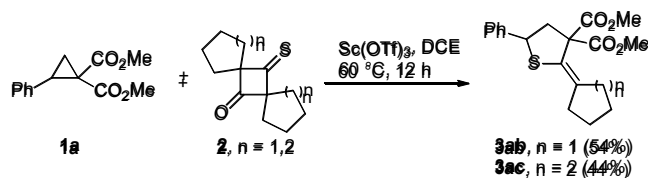
dimerization in good yields. As shown in Scheme 3 five- and six-membered carbocycles were attached to the semicyclic double bond system. A slight decrease of the yield was observed with increasing ring size.

Scheme 2. Scope with Regard to Donor-Acceptor Cyclopropanes^a



^aReaction conditions: **1** (100 μmol), **2a** (200 μmol), Sc(OTf)₃ (10 mol %), DCE (2.5 mL), under Ar, 60 °C, 12 h; yields represent isolated and purified products; DCE = dichloroethane

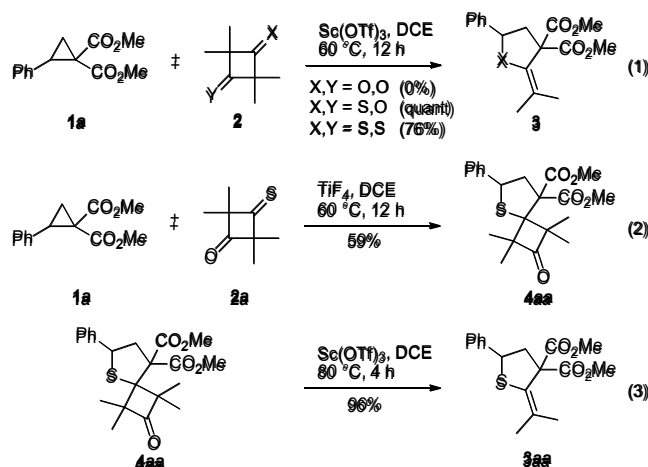
Scheme 3. Scope with Regard to the 3-Thioxocyclobutanone Motif^a



^aReaction conditions: **1a** (200 μmol), **2** (400 μmol), $\text{Sc}(\text{OTf})_3$ (10 mol %), DCE (5.0 mL), under Ar, 60°C , 12 h; yields represent isolated and purified products; DCE = dichloroethane

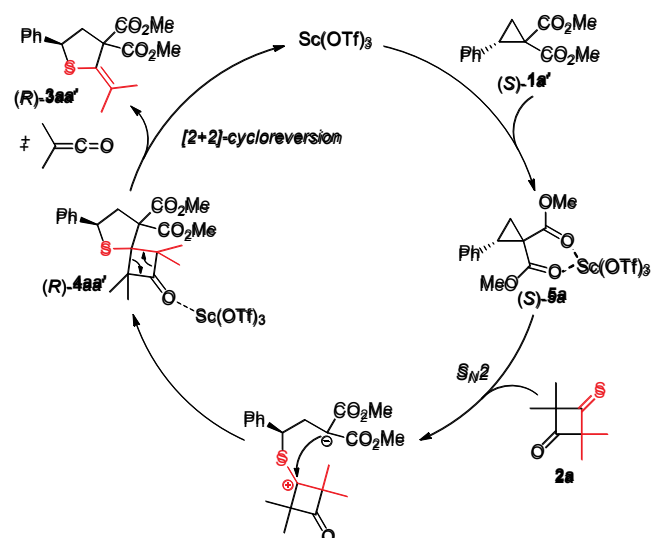
To get deeper insights into the reaction mechanism, we carried out several control experiments (Scheme 4). First, we were interested whether a ketone or a ketene moiety would also be able to insert. Therefore, we employed diketone **2a'**, which was subjected to the general reaction conditions. In this experiment, no conversion of cyclopropane **1a** was observed. On using dithioketone **2a''** a complex mixture resulted, but we were able to isolate crude **3aa** in 76% yield (Scheme 4, eq 1). Next, we observed that spiro compound **4aa** was obtained in 59% yield if one uses TiF_4 as Lewis acid (Scheme 4, eq 2). This observation strengthened our hypothesis that the thiocarbonyl inserts first, followed by the release of dimethylketene, and this assumption was proved by another experiment. Compound **4aa** was subjected to the general reaction conditions; compound **3aa** resulted in nearly quantitative yield (Scheme 4, eq 3). Interestingly, no conversion of **4aa** was observed if the reaction was run without $\text{Sc}(\text{OTf})_3$ as Lewis acid. To prove the formation of dimethylketene the reaction was performed in presence of phenol as trapping reagent. GC-MS analysis showed indeed the desired trapping product (see Supporting Information).

Scheme 4. Control Experiments



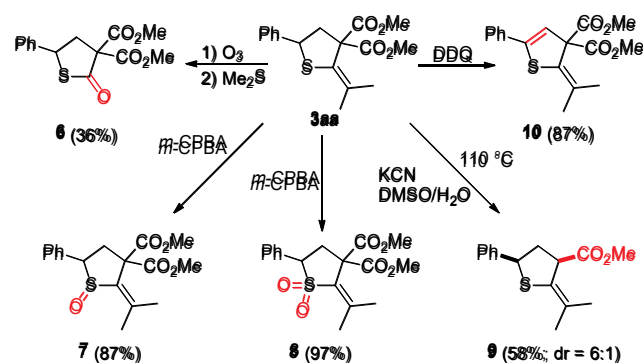
As corroborated by our control experiments, we propose the following reaction pathway (Scheme 5). $\text{Sc}(\text{OTf})_3$ activates cyclopropane (*S*)-**1a'** by interacting with the geminal diester moiety to allow an $\text{S}_\text{N}2$ -type nucleophilic attack of the thioketone **2a**, followed by a ring-closure to intermediate (*R*)-**4aa'**.¹² Coordination of $\text{Sc}(\text{OTf})_3$ to the oxygen of the ketone paves the way for the terminating cleavage of dimethylketene,¹³ whereby product (*R*)-**3aa'** is released and $\text{Sc}(\text{OTf})_3$ is able to undergo the next catalytic cycle.

Scheme 5. Proposed Mechanism



The utility of the formal thioketene insertion was demonstrated by selected further transformations (Scheme 6). Undecorated thioenol ether derivative **3aa** was subjected to ozonolysis to furnish thiolactone **6** in 36% yield. Oxidation with equimolar amounts of *m*-CPBA delivered sulfoxide **7** (87%), whereas full oxidation with an excess of *m*-CPBA resulted in nearly quantitative formation of sulfone **8**. Krapcho decarboxylation with KCN in wet DMSO afforded monoester **9** in moderate yield and a diastereomeric ratio of 6:1 with the *cis*-isomer being favored. Treatment with DDQ initiated an elimination reaction to furnish dihydrothiophene **10** in 87% yield.

Scheme 6. Follow-Up Chemistry



In summary, we have developed a new process for the formal insertion of thioketenes into D-A cyclopropanes under Lewis acid catalysis. 3-Thioxocyclobutanone derivatives were successfully utilized as thioketene surrogates and led to a broad scope of sulfur-containing heterocycles with a semicyclic thioether moiety. Furthermore, additional experiments gave hints of a mechanism that follows a formal $[3+2]$ -cycloaddition and a subsequent $[2+2]$ -cycloreversion releasing dialkyl ketene.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, analytical data for all new compounds (PDF), crystal data for **3aa** (CIF).

AUTHOR INFORMATION

Corresponding Author

E-mail: d.werz@tu-braunschweig.de

ORCID

André U. Augustin: 0000-0002-6425-2843

Daniel B. Werz: 0000-0002-3973-2212

Notes

The authors declare no competing financial interest.

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